

SPECIAL ARTICLE

Tranexamic Acid in the Management of Upper Gastrointestinal Bleeding: an Evidence-based Case Report

Nur Atikah¹, Gurmeet Singh², Hasan Maulahela², Rahmat Cahyanur²

¹ Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

² Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Correspondence mail:

Nur Atikah. Jl. Percetakan Negara VIII No. 40 A, Jakarta 10570, Indonesia. email: nur.atikah28@gmail.com.

ABSTRAK

Tujuan: mengetahui efektivitas penggunaan asam traneksamat, yang dikatakan dapat menurunkan mortalitas lebih baik daripada plasebo. **Metode:** melalui penelusuran literatur di Cochrane Library, PubMed, Clinical Key, EBSCO, Science Direct dan Proquest sesuai dengan pertanyaan klinis, didapatkan satu systematic review yang mengkaji tujuh randomized controlled trials. Melalui telaah kritis, disimpulkan bahwa artikel tersebut memenuhi kriteria validitas dan relevansi. **Hasil:** artikel tersebut menemukan bahwa tidak ada perbedaan yang jelas antara kelompok intervensi dengan kelompok placebo dalam hal mortalitas. **Kesimpulan:** asam traneksamat tidak direkomendasikan untuk menurunkan mortalitas pada pasien perdarahan gastrointestinal bagian atas.

Kata kunci: asam traneksamat, mortalitas, perdarahan gastrointestinal bagian atas.

ABSTRACT

Aim: to review the effectiveness of tranexamic acid therapy which has been proposed to reduce bleeding and in turn lower mortality rate. **Methods:** following literature searching based on our clinical question on Cochrane Library, PubMed, Clinical Key, EBSCO, Science Direct and Proquest, one systematic review that includes seven randomized controlled trials is obtained. The article meets validity and relevance criteria. **Results:** the systematic review found that there is no any clear evidence between intervention and control groups in term of mortality. **Conclusion:** the use of tranexamic acid to reduce mortality in patients with upper gastrointestinal bleeding is not recommended.

Key words: tranexamic acid, mortality, upper gastrointestinal bleeding.

INTRODUCTION

Upper gastrointestinal bleeding includes hemorrhage from the esophagus to the ligament of Treitz and has life-threatening potential.^{1,2} UK National Audit in 2007 shows that peptic ulcers accounted for 36% of all causes of upper gastrointestinal bleeding.³ Common clinical manifestations are hematemesis, coffee-ground emesis and melena.^{4,5} Despite advances in therapy, mortality rate remains unchanged at

7 to 10% due to advances in patient age, more co-morbid diseases, and recurrent bleeding.^{3,6}

Biopsy samples from patients with gastric or duodenal ulcer showed a significant increase in fibrinolytic activity compared to patients without gastric or duodenal ulcer ($p < 0.05$).⁷ Tranexamic acid is an anti-fibrinolytic agent that slows down the conversion of plasminogen to plasmin. Therefore, it prevents the breakdown of blood clots, resulting in hemostasis.⁵ Several hospitals

routinely use tranexamic acid for patients with upper gastrointestinal bleeding although guidelines have not generally recommended it.⁸ Antifibrinolytic agents such as tranexamic acid are expected to reduce fibrinolytic activity, thus prevent recurrent bleeding and mortality.

CLINICAL QUESTION

A 59-year-old woman came to the emergency unit complaining of dark-colored vomit since one hour before admission. She also felt nausea and heartburn along with passing black stools once. The patient had a history of dyspepsia since five years prior. Endoscopic examination found giant duodenal ulcer (Forest Ib) and erosive gastritis. Her physician recommended administration of intravenous tranexamic acid 500 mg thrice

daily as a part of her upper gastrointestinal bleeding treatment. Thus, we formulate the following clinical question: In patients with upper gastrointestinal bleeding, does the use of tranexamic acid reduce mortality compare to without tranexamic acid?

METHODS

Literature searching was done on November 17, 2013 in these databases: Cochrane Library, PubMed, Clinical Key, EBSCO, Science Direct and Proquest. Keywords used were “tranexamic acid”, “upper gastrointestinal bleeding” and “mortality”. The results are presented in **Figure 1**.

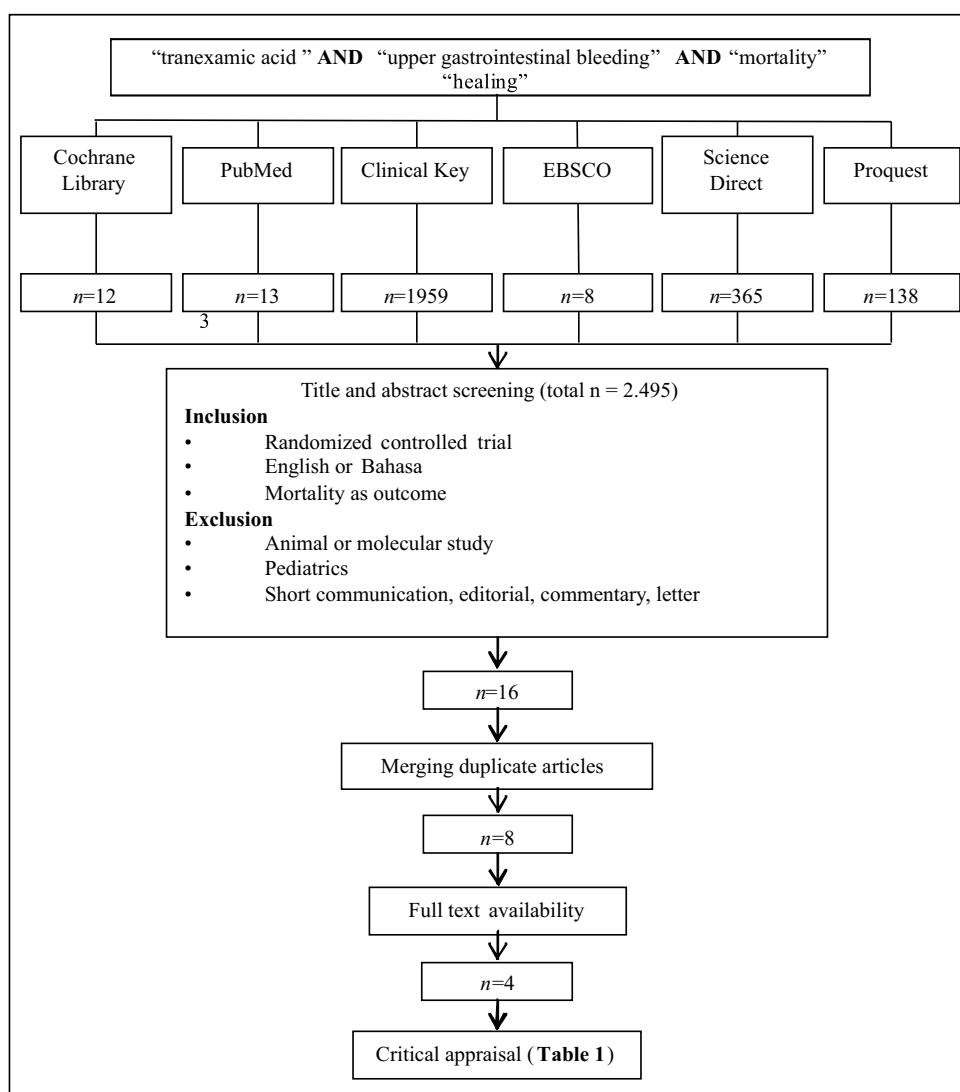


Figure 1. Flow chart of literature searching

RESULTS

Four eligible articles consisting of two original articles and two systematic reviews were obtained. Among these articles, one systematic review study, Gluud et al.⁶, already covered the remaining available articles (Gluud et al.⁸, Biggs et al.⁹, Hawkey et al.¹⁰) with one systematic review (Gluud et al.⁸) as an earlier version of the other systematic review (Gluud et al.⁶). **Table 1** shows the process of critical appraisal based on guidelines by Center for Evidence-Based Medicine University of Oxford.

Gluud et al.⁶ reviewed seven double-blind randomized controlled trials published from 1973 to 2001. The sources of bleeding in these trials are peptic ulcers (mean proportion 59%, range 27% to 90%) and esophageal varices (mean proportion 8%, range 5% to 16%). Three trials use oral tranexamic acid only, whilst the remaining trials use intravenous tranexamic acid for a maximum of two days or until endoscopy was performed, followed by oral medication. Duration of treatment ranges from two to seven days with total daily dose ranges from 4 to 8 g. The total dose of tranexamic acid given for the entire treatment period ranges from 16 to 42 g.

Five of seven trials report to have lost-to-follow-up subjects, while the remaining do not have any drop-out subjects. The number of patients initially randomized is 1645. One among five subjects (21%) was excluded after initial randomization due to lack of verified bleeding, presence of malignant disease, terminal illness, late administration of treatment, or late admission to the hospital. Worst case scenario

and post hoc sequential analysis are performed to evaluate any potential influence of lost-to-follow-up subjects.

As many as 41 of 829 patients (5%) in tranexamic acid group and 68 of 825 patients (8%) in placebo group passed away. Random effect model meta-analysis found that tranexamic acid reduces mortality (RR 0.61; 95% CI 0.42 – 0.89; I²=0%). Regression analysis found no clear evidence of bias (p=0.527). Different result is obtained when the proportion of patients who were excluded after randomization is counted. Worst case scenario analysis found no clear differences between intervention and control groups in terms of mortality (RR 0.78; 95% CI 0.58-1.05; I²=6%). In addition, post hoc analysis found that overall sequential results are not significant after repeated testing.

DISCUSSION

On tissue injury, activation of the coagulation cascade leads to the formation of thrombin, which cleaves fibrinogen to fibrin. These polymerize to form insoluble fibrin and produce a haemostatic seal on damaged blood vessel walls. The fibrinolytic system is activated by the deposition of fibrin and assists in keeping the vessel lumen open. Fibrinolysis occurs when plasminogen binds to lysine residues on the surface of fibrin and is converted to plasmin in the presence of plasminogen activator. Plasmin cleaves fibrin into fibrin degradation products that inhibit excessive fibrin formation.¹¹

Lysis of a excessive formed fibrin clot is an likely to be important in the clinical setting

Table 1. Critical Appraisal*⁶

Author	Validity						Relevance			
	Clear clinical question	Probable missed study	Eligibility criteria	Appraising studies validity	Study to study consistency	Discussion	Domain	Determinant	Outcome	Level of evidence
Gluud et al (2012)	+	+	+	+	+	+	+	+	+	1a

+ stated clearly in the article; - not being done; ? not stated clearly

*appraisal guideline for systematic review was adopted from Center for Evidence Based Medicine University of Oxford

of upper gastrointestinal bleeding.¹² Previous studies had found that fibrinolytic activity has been detected in gastric and duodenal tissues which contain high concentration of plasminogen activators. Vreebur et al.⁷ found that mucosal fibrinolytic activity is enhanced in mucosal biopsies from patients with an ulcer with endoscopic sign of bleeding.⁷

Tranexamic acid is a synthetic lysine amino acid derivative that has antifibrinolytic activity which acts by blocking the lysine binding sites of the plasminogen molecule that are essential for its binding to fibrin. With its high affinity lysine binding site of plasminogen, tranexamic acid is expected to reduce recurrent bleeding on upper gastrointestinal bleeding.¹¹ However, Gluud et al.⁶ found no clear evidence regarding the effect of tranexamic acid in reducing mortality in patients with upper gastrointestinal bleeding.⁶ Study conducted by Patchett et al.¹² found that gastric juice is also contributes to gastrointestinal bleeding. Pure gastric juice interferes with haemostasis both by delaying the rate of clot formation and by reducing the quality of the final clot formed. This study suggests that an acid dependent factor in gastric juice such as a gastric protease is responsible in impairing clot formation. Thus, although tranexamic acid may be capable of inhibiting the plasmin mediated pathway, it has no activity against non-specific protease mediated clot lysis in patients with upper gastrointestinal bleeding.

The systematic review conducted by Gluud et al.⁶ does not have enough information about the side effect of tranexamic acid. Although the study did not find significant correlation between tranexamic acid and the risk of thromboembolism events, the analysis does not have sufficient statistical power to make clear inferences. Theoretically, tranexamic acid increases the risk of thrombosis due to unopposed fibrin generation.

CONCLUSION

There is no clear evidence regarding the effect of tranexamic acid in reducing mortality in patients with upper gastrointestinal bleeding. Because of the limited validity of both internal and external evidence, additional randomized

controlled trial is needed to establish the effect of tranexamic acid in combination with current clinical practice. Thus, the current use of tranexamic acid as routine therapy in upper gastrointestinal bleeding is still not recommended.

REFERENCES

1. Wilkins T, Khan N, Nabh A, et al. Diagnosis and management of upper gastrointestinal bleeding. *Am Fam Physician*. 2012;85:469-76.
2. British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: guidelines. *Gut*. 2002;51:iv1-iv6.
3. Lau YW, Barkun A, Fan D, et al. Challenges in the management of acute peptic ulcer bleeding. *Lancet*. 2013;381:2033-43.
4. Albeldawi M, Qadeer MA, Vargo JJ. Managing acute upper GI bleeding, preventing recurrences. *Cleve Clin J Med*. 2010;77:131-42.
5. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med*. 2008;359:928-37.
6. Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database of Systematic Reviews*. 2012;Issue 1.
7. Vreeburg EM, Levi M, Rauws EAJ, et al. Enhanced mucosal fibrinolytic activity in gastroduodenal ulcer haemorrhage and the beneficial effect of acid suppression. *Aliment Pharmacol Ther*. 2001;15:639-46.
8. Gluud LL, Klingenberg SL, Langholz E. Systematic review: Tranexamic acid for upper gastrointestinal. *Aliment Pharmacol Ther*. 2008;27:752-8.
9. Biggs JC, Hugh TB, Dodds AJ. Tranexamic acid and upper gastrointestinal haemorrhage - a double-blind trial. *Gut*. 1976;17:729-34.
10. Hawkey GM, Cole AT, McIntyre AS, et al. Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points. *Gut*. 2001;49:372-9.
11. McCormac PL. Tranexamic acid: a review of its use in treatment of hyperfibrinolysis. *Drugs*. 2012;72(5):585-617.
12. Patchett SE, O'Donogue DP. Pharmacological manipulation of gastric juice: thrombelastographic assessment and implications for treatment of gastrointestinal haemorrhage. *Gut*. 1995;36:358-62.